REMARKS

A. Claim Amendments.

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim 18 is currently being amended. The amendment changes the location of wording present in the previously presented version of Claim 18 and adds limitations from Claim 23, now canceled. No new subject matter being added, entry of the claim amendment is therefore requested.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 18-19 and 22-24 are now pending in this application.

B. Response to Enablement Rejection of Claims 18-19, 23-24, 32 and 34-35.

Applicants understand the basis of the enablement rejection to be that, although expression of phospholamban mutants followed by a corresponding decrease in calcium transients in myocytes is demonstrated by data in the Specification, it has "provided guidance to override the issue of unpredictability of treating heart failure by PLB gene therapy...," especially as to "extrapolating results in specific animal models." (Action at page 8). In particular, the Action questions whether the invention is enabled sufficiently to provide a "treatment with a *cure* effect" (Action at page 9, emphasis added). In that respect, it is asserted that additional clinical research is required (*id.*, citing Zhao, et al.).

Applicants respectfully traverse the rejection on the grounds that (1) the claims are not directed to a cure for heart failure, but instead to influencing a specific metabolic process in the heart that is known to be physiologically related to heart failure; (2) enablement cannot be evaluated on the basis of whether clinical results in humans have or can be demonstrated; and (3) the most pertinent art of record establishes that the Specification provides the art with a reasonable expectation that the invention can be practiced as claimed without undue experimentation and, as such, the invention is enabled.

Firstly, the invention claimed is not asserted to be a cure for heart disease. Rather, it is a treatment that beneficially affects SERCA2 function whose physiological relationship to improving cardiac function in heart failure is well known (see, e.g., the inventors' prior issued patent to SERCA2 mediated gene therapy; US Pat. No. 6,605,274; concerning the interaction between phospholamban and SERCA2, see the discussion in the present Specification at page 2, line 16 through page 5, line 6). To that end, the Specification states that the invention provides "methods for treatment of heart failure by inhibiting the effect of phospholamban on [SERCA2 mediated] Ca^{2+} uptake in cardiac tissues." (Specification page 6, lines 10-12). The art agrees that the invention, as described, does provide the asserted improvement in SERCA2-mediated function in the heart:

> The achievement of Chien and his colleagues is significant in two ways. First, while heart failure can wax and wane, it is a chronic condition requiring persistent therapy. The new study is the first to demonstrate that gene therapy can achieve this. **Second, this study shows that enhancement of SERCA function can be used to treat heart failure caused by other defects.**" (Crystal, *Gene Therapy*, 10:2-3 (2003), at 3; emphasis added).

The foregoing comment was made with respect to the inventors' post-filing published description of the invention as now disclosed and claimed. Thus, whatever concerns the art may or may not have about whether phospholamban gene therapy will work for cardiac conditions

generally, those of skill in the art clearly consider the question to have been resolved for the particular approach taken by the invention to treat heart failure.

The next issue raised in the Action concerns whether the invention as described is ready for clinical use. In this respect, the Action cites Crystal, supra, as acknowledging that the art was not ready to commence human heart failure gene therapy trials as of early 2003 (Crystal at p. 3; Office Action at p. 8). Zhao, et al. is also cited as being "cautiously optimistic" about the clinical prospects for the invention, subject to further research. (Zhao, et al. at p. 214; Office Action at p. 9).

Applicants respectfully submit that the clinical status of the invention for use in humans is not pertinent to the question of whether the claimed invention is enabled. Clinical efficacy and safety are not issues within the purview of the Patent Office, but are instead exclusively matters of concern to the Food and Drug Administration (*Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed.Cir. 1994)). Moreover, the fact that further experimentation may be required to advance the invention into human use, even if true, does not establish that the invention is not enabled.

With respect to enablement, the question is not whether further experimentation with the invention is required—it very often will be. Rather, the question is only whether one skilled in the art can make use of the claimed invention coupled with information known in the art without "undue" experimentation. *Genentech, Inc. v. Novo Nodisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997), see also MPEP §2164.01(c), fourth paragraph. In *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998), the Federal Circuit confirmed that *routine* experimentation does not constitute *undue* experimentation:

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a

> reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention as claimed.

Id., citing *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564; 37 USPQ2d 1618, 1623-24 (Fed. Cir. 1996); see also, *In re Wands*, 858 F.2d 731, 736 40 (Fed. Cir. 1988).

With respect to gene therapy directed at SERCA2 function in the heart, only two potential avenues for further experimentation are noted in the art of record as predicates for human clinical use of such therapy: the identification of optimal promoters for expression vectors (Crystal, supra at 3) and, for initial studies, the use of sufficiently informative animal models (Zhao, supra at 214-215, bridging paragraph). In the first respect, while efforts to improve available expression constructs are ongoing in the gene therapy art, viral constructs of the kind utilized by the inventors have been used in the heart from a time preceding the filing date of the present application[1], and have been approved by the FDA for human clinical trial use in SERCA2 gene therapy (see, e.g., clinical trial NCT00454818, Phase I, www.clinicaltrials.org). Therefore, while further improvements to gene therapy expression vectors are desirable, the constructs existing at the time the present application was filed were sufficient to enable the art to practice the invention without undue experimentation.

[1] See, e.g., U.S. Patent No. 6,605,274, filed April 1995, claiming a method for SERCA2 gene therapy using adenoviral vectors; U.S. Patent No. 5,797,870, filed March 1995, claiming a method for introducing a "gene therapy agent" into the pericardium using expression vectors such as adenoviral vectors and adeno-associated virus vectors; U.S. Patent No. 5,919,449, filed May, 1995 claiming an *ex vivo* method for implantation of porcine cardiomyocytes transfected with a viral expression vector into the heart, to treat conditions such as congestive heart failure; U.S. Patent 6,162,796, filed September, 1995, describing use of AAV vectors in particular to deliver therapeutic genes to the heart to treat cardiac disorders; and, U.S. Patent No. 6,306,830, filed September, 1996, identifying vectors desirable for use in treating congestive heart failure as including then known adenoviruses, adeno-associated viruses, and retroviruses.

With respect to animal models for heart failure, including those used by the inventors, it is respectfully submitted that the comments of the Crystal and Zhao, et al. authors cited at pages 8 and 9 of the Office Action have been misunderstood. Crystal did suggest "caution in extrapolating results in specific animal models" (Action at page 8), but his comments weren't directed to the inventors' work. Rather, the full quotation from the Crystal paper reveals that his comment was directed at a different study, where results obtained from use of an antibody in animal hearts couldn't be duplicated in humans ("[t]he lack of success in human trials of an antibody treatment that prevents heart failure in a murine model suggests that we need to be cautious in extrapolating results in specific animal models." (Crystal, supra at page 3)).

In contrast, with respect to the inventors' work, Crystal said only that while the results in the BIO14.6 hamster model of cardiomyopathy succeeded in enhancing "a variety of parameters associated with cardiac function," there "may be other important abnormalities not present in this animal model that also need to be corrected." (p. 3, emphasis added). In other words, although other physiologic features of heart failure may also need to be addressed for full clinical benefit, the inventors' work in the hamster model did establish the premise set forth in the present application; i.e., that "SERCA2 is sufficiently central to cardiac function and that enhancing its activity at least partially overrides other abnormalities." (*Id.*). Zhao, et al. agreed: "...Chien and colleagues have reported that chronic inhibition of PLN [phospholamban] by delivering a pseudophosphorylated S16E-PLN into the heart [to] successfully prevented progressive heart favilure in inhereited cardiomyopathic hamsters, and also rescued the cardiac dysfunction and remodeling induced by myocardial infarction, in a model of acquired heart failure." (supra, at 214).

Zhao, et al. did express some concerns about *other* animal models of cardiac disease, principally regarding the degree to which results in mice could be extrapolated to demonstrate likely responses to therapy by human hearts, given differences in calcium processing by human and mouse hearts (p. 214-215, bridging paragraph). However, Zhao, et al.'s comments were not

specifically directed to the inventors' work in hamsters, which he regarded as validating the promise of phospholamban gene therapy (*ibid.*, at 214).

The inventors' initial work with the invention was in transgenic mice as described in the Specification. Based on the results obtained, the inventors concluded that the invention could be used to modify calcium handling by cardiomyocytes in heart failure. That premise was then validated by the inventors *using the same therapeutic modality described in the Specification and now claimed* in another art-accepted model (the hamster model of cardiomyopathy). As noted by Crystal and Zhao, et al., the hamster work corroborated the promise of the invention to the satisfaction of the art. Such post-filing evidence that the invention was as claimed establishes enablement (see, e.g. MPEP § 2164,05). By definition, therefore, the Specification enables the art to practice the invention without undue experimentation.

Based on the foregoing, Applicants respectfully submit that the Specification clearly and sufficiently teaches how to make and use both the S16E and K3E/R14E mutant molecules, each of which possesses the ability to suppress phospholamban activity, thereby increasing SERCA2 activity with the therapeutic implications for heart failure as described. Reconsideration and withdrawal of the enablement rejection is therefore warranted and requested.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application. A change of correspondent's address for the undersigned is also submitted herewith.

Check number 585491 in the amount of $620.00 is enclosed as payment for the Request for Continued Examination fee ($395.00) and the Petition for Two-Month Extension of Time fee ($225.00). No other fee is believed due in connection with this Amendment. If any additional fees are due, the Commissioner is hereby authorized to charge any fees that may be required by this paper to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is attached.

Respectfully submitted,

Date: April 23, 2007

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